Perioperative Stroke

Where Do We Go from Here?

This article has been selected for the ANESTHESIOLOGY CME Program. Learning objectives and disclosure and ordering information can be found in the CME section at the front of this issue.

IN this issue of ANESTHESIOLOGY, Mashour *et al.* present an extensive analysis of the prospectively collected American College of Surgeons National Surgical Quality Improvement Program (ACS-NSQIP) database. The authors investigated perioperative stroke in patients undergoing noncardiac nonneurologic surgery.[1] They analyzed more than 523,000 patients in the NSQIP database and developed a risk model to predict the occurrence of ischemic and hemorrhagic stroke. The model was derived from a cohort of approximately 350,000 patients and validated in a 173,000-patient cohort. The overall incidence of stroke in both cohorts was 0.1%. Perioperative stroke increased 30-day mortality by 8-fold (21% absolute risk increase of mortality in a comorbidity matched cohort).

Multivariate logistic regression revealed nine predictors of stroke and one protective factor. These 10 elements were used to create a risk model. The risk factors for stroke included: age 62 yr or older, myocardial infarction within 6 months of surgery, hypertension, history of stroke, history of transient ischemic attack, history of chronic obstructive pulmonary disease, dialysis, acute renal failure, and current tobacco use. Surprisingly, moderate obesity was protective (body mass index 35–40). There were no data regarding atrial fibrillation, other dysrhythmias, or hypotension in the NSQIP database, so these values could not be included. In the final unweighted model, stroke risk was 0.1% in patients with two or fewer risk factors, 0.7% in those with three or four risk factors, and 1.9% in the highest risk group with five or more risk factors. Despite the author's preference for a "simpler" unweighted risk classification, a *weighted* risk score would have been more precise, as the risk associated with the identified predictors varies considerably (hazard ratio range: 0.6–3.9).

How do we use these data? Even in the highest risk group identified by Mashour *et al.*, perioperative stroke was an uncommon adverse event (occurring in 1 in 50 patients) after noncardiac nonneurologic surgery. In fact, this high-risk population is elderly and sick and at risk for any of a large number of uncommon adverse events. The addition of atrial fibrillation to the risk assessment, if the data were available, would likely add predictive power but still not change the perioperative management of the individual patient. After all, any medically indicated anticoagulant and antiplatelet therapy should be restarted as soon as safely possible after surgery. Intraoperative hypotension should be treated aggressively. Thus, the anesthesiologist and surgeon are left with few practical options for preventing perioperative stroke beyond providing high-quality routine care.

So where do we go from here? Perioperative stroke is an uncommon complication with devastating consequences, as detailed by Mashour *et al.* Stroke is also a heterogeneous disease resulting from a multitude of etiologies.[2] Perioperative ischemic stroke can be caused by cardioembolism (from dysrhythmia or valvular disease), paradoxical embolism through a right to left cardiopulmonary shunt, artery-to-artery embolism, *in situ* thrombus formation in atherosclerotic cerebral vessels, or distal arterial watershed infarction from hypoperfusion. Venous infarction (ischemic or hemorrhagic) caused by cerebral sinus or cortical vein thrombosis can occur perioperatively in patients with hypercoagulability. Perioperative hemorrhagic stroke may be caused by hypertension or hemorrhagic transformation of an ischemic infarct, possibly exacerbated by antiplatelet or anticoagulant therapy. Finally, other neurologic outcomes such as cognitive dysfunction may be on a continuum with perioperative stroke, but there is insufficient evidence at this time to go beyond mere speculation.

Once again, where do we go from here? How do we prevent this serious uncommon complication that is multifactorial in etiology?

Better Data. First and foremost, this is a call for better prospective data gathering. The work of Mashour *et al.* illustrates the limitations of the NSQIP database, despite the laborious efforts of very dedicated nurses across the United States. Understanding uncommon events such as perioperative stroke will require detailed information on the entire spectrum of care from all surgical patients. The Centers for Medicare and Medicaid Services have mandated that electronic medical records meet meaningful use criteria and are providing financial incentives toward this end. This endeavor is currently accelerating the adoption of electronic medical records.* Although universal integration of various healthcare databases is likely decades away in the United

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* Dolan PL. American Medical News. EMR adoption rates up, with small practices left behind. Available at: http://www.ama-assn.org/amednews/2010/11/22/bisb1122.htm. Accessed February 4, 2011.

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States, large health systems should be able to accomplish this within the next 5 yr. Direct note entry by physicians, midlevel providers, and nurses into queryable informatics systems will allow researchers to create much higher level analyses. The NSQIP stroke patients undoubtedly saw a neurologist and underwent imaging studies, cardiac assessments, rhythm monitoring, and review of intraoperative hemodynamic variables and were on various regimens of antiplatelet, anticoagulant, antihypertensive, and statin therapies. However, none of these data are routinely obtainable for research. This information would have likely created a very different predictive model and conclusions regarding at risk populations.

With better risk assessments, patients at high risk of perioperative stroke (more than 10%, for example) could be studied prospectively in reasonably sized yet adequately powered trials investigating new preventive interventions. Statins, antiplatelet and anticoagulant regimens, and antiinflammatory and novel neuroprotectant therapies could be pursued. Intraoperative neuromonitoring, such as with cerebral oximetry, might show benefit in patients at high risk of stroke. Modest hypertension may be beneficial intraoperatively. The Perioperative Ischemic Evaluation Study Trial demonstrated an increase in stroke with indiscriminant β-blockade.[3] However, in that study, only 60 strokes occurred in the more than 8,300 patients at risk for atherosclerotic disease. This finding highlights the need to identify an even higher risk cohort for inclusion in future trials to achieve the necessary event rates.

Genomic, proteomic, and metabolomic studies hold great promise for identifying high-risk individuals and diagnosing acute stroke. However, this field is still in its infancy despite more than a decade of research.[4,5] Connecting genotype to phenotype depends on large cohorts of patients with well-defined stroke syndromes. Known modifiable risk factors, such as diabetes and hypertension, only explain approximately two thirds of the risk for stroke.[4] Genetic mechanisms of stroke are known only for a few rare stroke syndromes such as cerebral autosomal dominant arteriopathy with subcortical infarcts and dementia, commonly known by the acronym CADASIL.[4] Genetic polymorphisms causing hypercoagulability, such as factor V Leiden, increase the risk for cerebral sinus thrombosis[4] and deep venous thrombosis, but account for a small number of perioperative strokes. We are still a long way from understanding the genomics and proteomics of common stroke syndromes.

What About Now? For the time being, physicians need to maintain vigilance for perioperative stroke. Neurologic function can be assessed at the bedside on routine examination, even by simply observing the patient's movements, speech, and cognition during a brief postoperative visit. Neurologic signs or symptoms should trigger stroke codes and stroke teams that can emergently triage patients for acute interventions such as thrombolysis (intravenous or intraarterial) and/or endovascular clot removal.[6,7] Immediate treatment is paramount as outcomes worsen with time from ictus; "time is brain."[8]

We must continue to search for answers to stroke and neurocognitive complications in the perioperative period. Our current databases are largely insufficient, and new approaches are needed. We applaud the determination of investigators, such as Dr. Mashour, to see this work move forward. Robert Frost published "Stopping by Woods on a Snowy Evening" in 1923.[9] That same year he was a visiting fellow in Ann Arbor, not far from University of Michigan Hospital where Mashour *et al.* currently practice.† So it seems fitting to remind the anesthesiology community now, nearly a century later, that we have "promises to keep, and miles to go before (we) sleep."[9]

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† Robert Frost. Wikipedia. Available at: http://en.wikipedia.org/wiki/Robert_Frost. Accessed February 4, 2011.

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Perioperative Stroke and Associated Mortality after Noncardiac, Nonneurologic Surgery

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ABSTRACT

Background: Stroke is a leading cause of morbidity and mortality in the United States and occurs in the perioperative period. The authors studied the incidence, predictors, and outcomes of perioperative stroke using the American College of Surgeons National Surgical Quality Improvement Program.

Methods: Data on 523,059 noncardiac, nonneurologic patients in the American College of Surgeons National Surgical Quality Improvement Program database were analyzed for the current study. The incidence of perioperative stroke was identified. Logistic regression was applied to a derivation cohort of 350,031 patients to generate independent predictors of stroke and develop a risk model. The risk model was subsequently applied to a validation cohort of 173,028 patients. The role of perioperative stroke in 30-day mortality was also assessed.

Results: The incidence of perioperative stroke in both the derivation and validation cohorts was 0.1%. Multivariate analysis revealed the following independent predictors of stroke in the derivation cohort: age ≥62 yr, history of myocardial infarction within 6 months before surgery, acute renal failure, history of stroke, dialysis, hypertension, history of transient ischemic attack, chronic obstructive pulmonary disease, current tobacco use, and body mass index 35–40 kg/m^2 (protective). These risk factors were confirmed in the validation cohort. Surgical procedure also influenced the incidence of stroke. Perioperative stroke was associated with an 8-fold increase in perioperative mortality within 30 days (95% CI, 4.6–12.6).

Conclusions: Noncardiac, nonneurologic surgery carries a risk of perioperative stroke, which is associated with higher mortality. The models developed in this study may be informative for clinicians and patients regarding risk and prevention of this complication.

What We Already Know about This Topic

- Stroke is a potentially devastating perioperative complication, even after surgeries not involving the heart or great vessels

What This Article Tells Us That Is New

- Perioperative stroke in the low-risk population varies with surgical procedure, has a number of independent predictors including history of stroke or transient ischemic attack, and is associated with an eight-fold increase in mortality

STROKE is a leading cause of morbidity and mortality in the United States and is known to occur in the perioperative period.[1] Perioperative stroke is primarily associated with major cardiovascular procedures[2] but has also been reported after general surgery.[3,4] A recent study of acute ischemic stroke in the noncardiovascular population using an

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administrative database found an incidence of 0.7% after hemicolectomy, 0.2% after hip replacement, and 0.6% after lobectomy or segmental lung resection.[5] In the population 65 yr and older, the incidence rose to 1.0%, 0.3%, and 0.8%, respectively. Importantly, perioperative stroke was associated with increased mortality.

Risk factors for perioperative stroke include renal disease, atrial fibrillation, valvular disease, congestive heart failure, hypertension, carotid disease, history of tobacco use, and history of stroke.[3–8] However, the assessment of risk factors for perioperative stroke has been restricted to case series,[9,10] case-control studies,[1,11] or large retrospective studies,[7] including those using administrative data.[5] Prospective studies have been limited because of the low incidence of the event in the noncardiovascular, nonneurosurgical population.[12] Thus, the objective of the current study was to assess the incidence and predictors of perioperative stroke and its role in mortality in a broad range of noncardiac, nonneurosurgical cases using a large, prospectively gathered clinical data set derived from the American College of Surgeons National Surgical Quality Improvement Program (ACS NSQIP).

Materials and Methods

General ACS NSQIP Methodology

Institutional Review Board approval (University of Michigan, Ann Arbor) was obtained for the analysis of these prospectively collected data, which are deidentified and publicly available. The ACS NSQIP methodology has been described elsewhere[13] and is summarized here. Operations requiring general, epidural, or spinal anesthesia are prospectively divided into 8-day cycles. At most institutions, the first 40 general surgery and vascular surgery operations within each 8-day cycle are included. At some ACS NSQIP institutions, additional cases outside of the general and vascular population may be analyzed. Procedures performed by cardiac, neurosurgery, orthopedic, urology, otolaryngology, plastics, thoracic, and gynecology services are a minority of the overall patient enrollment at these institutions.

For each operation, a trained surgical clinical reviewer, typically a registered nurse, prospectively collects preoperative patient demographics, preoperative comorbidities, operative information, selected intraoperative elements, laboratory values, and postoperative adverse events occurring as long as 30 days after the operation. Approximately 135 variables are collected for each enrolled patient. Surgical clinical reviewers complete standardized and detailed training regarding the definitions of study variables and must pass a written test with 90% accuracy to be approved as participants in ACS NSQIP. Regular conference calls, annual meetings, and site visits are used to maintain data reliability. Interrater reliability audits are performed in the first year of a site's participation and every other year afterward, with additional audits performed if a site fails an audit. The audit process consists of a manual review of 12–15 ACS NSQIP records at each site. A site visitor from the central ACS NSQIP offices reviews approximately 106 variables for each of these records and abstracts the data per ACS NSQIP definitions. Disagreements between the visitor abstracted data and the site's submitted data are identified. In 2008, the overall disagreement rate for the 140,132 variables audited was 1.36%.[14]

The ACS NSQIP participant use data file is a compilation of operations from 250 participating U.S. medical centers for the 4-yr period 2005–2008. It contains data from 211 non-Veterans Administration hospitals in the private sector and includes data from academic medical centers, large non-teaching hospitals, and community hospitals.§ To maintain institutional, provider, and patient anonymity, no site- or region-specific data elements are included in the participant use data file. Sites with interrater reliability audit scores demonstrating ≥5% disagreement are excluded from the ACS NSQIP participant use data file.

§ A list of ACS NSQIP participating institutions is available at https://acsnsqip.org/main/about_sites.asp. Accessed August 8, 2010.

ACS NSQIP Study Population and Variables Analyzed

Inclusion and Exclusion Criteria. General surgery, orthopedics, urology, otolaryngology, plastics, thoracic, minor vascular, and gynecology cases were included in this study as representative of being at low risk for perioperative stroke; cardiac, major vascular, and neurosurgical procedures were excluded as high risk. We also excluded patients who had disseminated cancer, a body mass index (BMI) less than 18.5 kg/m^2, or a documented 10% weight loss because this population represents high risk for stroke (due to hypercoagulability), brain metastasis with hemorrhage, and mortality.

Outcomes. Postoperative stroke and 30-day mortality were analyzed as the primary and secondary outcomes of interest, respectively. "Postoperative stroke" is defined by ACS NSQIP as an embolic, thrombotic, or hemorrhagic cerebrovascular event with patient motor, sensory, or cognitive dysfunction that persists for 24 h or more and occurs within 30 days of an operation. Thirty-day mortality can be from any mechanism of death, and the cause of death is not reported.

Patient Variables. Basic demographic data were analyzed, including age, sex, race, BMI, and American Society of Anesthesiologists physical classification status. Patient characteristics included diabetes mellitus (oral or insulin therapy), current tobacco use, history of chronic obstructive pulmonary disease requiring chronic bronchodilator therapy, congestive heart failure within 30 days before surgery, history of myocardial infarction within 6 months before surgery, hypertension requiring medication, acute renal failure, dialysis dependence, history of transient ischemic attack, and history of stroke. For history of stroke, we collapsed the ACS NSQIP categories "cerebrovascular accident with neurologic deficit" and "cerebrovascular accident without neurologic deficit" into a single category for the purpose of analysis. The "neurologic deficit" is defined by ACS NSQIP as "persistent residual motor, sensory, or cognitive dysfunction."

Statistical Analysis

Statistical analysis was performed using PASW Statistics 18 (SPSS Inc., Chicago, IL). Patients meeting the inclusion criteria were randomly assigned to a derivation cohort (67%) or validation cohort (33%). The derivation cohort was used to develop a nonparsimonious logistic regression model and risk index classification system for predicting postoperative stroke. The validation cohort was used to assess the validity of the model. Descriptive statistics were performed on all categoric and continuous data elements using either Pearson chi-square or Student's *t* test when appropriate to determine associations with postoperative stroke.

Collinearity diagnostics and Pearson correlations were evaluated for all preoperative variables in the derivation cohort. To facilitate the use of continuous variables in a risk index classification system, age was transformed into a dichotomous variable. This was achieved by identifying the maximum sensitivity plus specificity using a receiver operating characteristic (ROC) curve. The continuous variable BMI was separated into categories based on definitions of normal weight (BMI 18.5–24.9 kg/m^2), overweight (25.0–30.0 kg/m^2), obese I (30.1–34.9 kg/m^2), obese II (35.0–40.0 kg/m^2) and morbidly obese (more than 40.0 kg/m^2). White race was compared with Hispanic, black, American Indian or Alaska Native, and Asian or Pacific Islander. Diabetes oral therapy and diabetes insulin therapy were compared with "no diabetes." All variables were entered into a nonparsimonious (full model fit) logistic regression model to identify significant independent predictors of perioperative stroke in the derivation cohort. Patients with missing data (primarily racial demographics) were excluded from the regression. Variables with *P* values less than 0.05 were considered independent predictors.

The derivation model's predictive value was evaluated using ROC area under the curve (AUC).[15] Effect size for each independent predictor was evaluated using the adjusted odds ratio. We further validated the model using the bootstrap method (R statistical package, version 2.12; Bell Laboratories, Murray Hill, NJ). This method estimates a correction for overfitting in the model to derive estimates of predictive accuracy if applied to a comparable patient population.[16] Somers' Dxy estimates the difference in the probability of concordance and discordance between predicted and observed outcomes for all possible pairs of patients.[16,17] One hundred random samples with replacement were used and tested against the original sample.

For the unweighted risk score, a patient received one point for each independent risk factor identified by logistic regression; because of the protective effect identified for BMI 35.0–40.0 kg/m^2, patients received −1 point if they fell into that BMI category. In addition, a weighted risk score was developed based on the β coefficient in the nonparsimonious logistic regression model. To calculate the weighted score for each independent predictor, the β coefficient was divided by the smallest β coefficient of the independent predictors, multiplied by 2, and rounded to the nearest integer. The unweighted and weighted risk scores for the derivation cohort were compared using ROC AUC. If the ROC AUC of the unweighted and weighted risk scores overlapped in their 95% CI, the unweighted score was used for risk classification. We deemed this to be more clinically useful because the anesthesia provider would not need to recall the actual weighted value of each individual risk factor, only the overall number of risk factors. Thus, we chose the unweighted risk score to develop a risk index classification system.

Finally, to assess whether the occurrence of a postoperative stroke was associated with an increase in 30-day, all-cause mortality, we developed a risk-matched patient cohort for analysis. To minimize the effect of confounding preoperative comorbidities that increase the risk of not only 30-day mortality but also the primary outcome of stroke, we used the perioperative stroke propensity score from the nonparsimonious logistic regression model. The propensity score for each patient in the derivation cohort was the predicted probability (0–1) of experiencing the primary outcome, a perioperative stroke. Patients with a perioperative stroke were matched with patients who did not have a perioperative stroke using a three-digit propensity score that was created using the nonparsimonious logistic regression model. For each patient with a postoperative stoke, a patient with a matching three-digit propensity score was randomly selected from the nonstroke group. The quality of matching was evaluated with univariate analysis. After the matching, we assessed the association between perioperative stroke and 30-day, all-cause mortality using a Pearson chi-square test. The effect size is reported as odds ratio and 95% CI.

Results

Incidence of Perioperative Stroke

A total of 635,265 patients were in the ACS NSQIP database; 523,059 patients were in the noncardiac, nonmajor-vascular, and nonneurologic low-risk surgical cohort for this study. The most common surgeries performed in this population and the associated incidence of stroke are shown in table 1. Patients within this low-risk population were randomly allocated to a derivation cohort of 350,031 patients and a validation cohort of 173,028 patients. The incidence of perioperative stroke in the derivation cohort was 485 of 350,031 or 0.1%. Table 2 demonstrates demographics and univariate associations with perioperative stroke in the low-risk derivation cohort. The incidence of stroke in the validation cohort was 229 of 173,028 or 0.1%.

Independent Predictors of Postoperative Stroke and Risk Score

Collinearity diagnostics did not demonstrate a condition index above 30, so no bivariate correlation matrix was needed. Thus, all variables in table 2, except American Society of Anesthesiologists classification, were entered into the nonparsimonious logistic regression model with perioperative

Table 1. Common Procedures in the Derivation Cohort and the Associated Stroke Incidence

	Stroke All Age, % (n)	Stroke Age ≥65 yr, % (n)
Procedures in ACS NSQIP studied in Bateman *et al.*		
Hip arthroplasty (N = 1,568)	0.4 (6)	0.5 (5)
Lung resection (N = 1,484)	0.3 (5)	0.7 (5)
Colectomy (N = 33,426)	0.4 (130)	0.7 (100)
Most common procedures		
Hepatobiliary: biliary tree (N = 43,289)	0.1 (36)	0.2 (23)
Excisional breast (N = 36,793)	0.0 (16)	0.1 (11)
Hernia: ventral/umbilical/incisional/other (N = 32,638)	0.1 (28)	0.3 (21)
Hernia: inguinal/femoral incisional mesh (N = 26,448)	0.1 (17)	0.1 (10)
Colorectal: appendectomy (N = 26,046)	0.0 (6)	0.2 (4)
Esophagogastric: bariatric (N = 23,766)	0.0 (5)	0.0 (0)
Head and neck: tumor (N = 20,057)	0.0 (7)	0.1 (3)
Minor vascular: chest/extremity (N = 5,883)	0.0 (2)	0.1 (1)
Small intestine: resection/ostomy (N = 5,860)	0.5 (27)	0.6 (14)
Small intestine: lysis of adhesions, other (N = 5,683)	0.3 (17)	0.7 (14)
Abdominal: exploration (N = 5,760)	0.5 (26)	0.9 (18)
Hepatobiliary: pancreas (N = 4,832)	0.3 (15)	0.5 (10)
Musculoskeletal: amputation (N = 4,800)	0.8 (37)	1.1 (29)
Esophagogastric: gastric (N = 4,749)	0.3 (16)	0.7 (12)
Esophagogastric: esophagus/gastric (N = 4,635)	0.0 (1)	0.1 (1)
Hysterectomy (N = 4,454)	0.1 (3)	0.2 (1)
Musculoskeletal: arthroscopy (N = 4,255)	0.0 (0)	0.0 (0)
Musculoskeletal: spine (N = 3,480)	0.1 (4)	0.3 (3)
Colorectal: abdominoperineal resection (N = 3,169)	0.2 (7)	0.5 (5)
Musculoskeletal: knee (N = 2,970)	0.1 (4)	0.2 (4)
Anorectal: abscess (N = 2,508)	0.0 (0)	0.0 (0)
Simple skin and soft tissue (N = 2,383)	0.3 (6)	0.6 (4)
Colorectal: low anastomosis (N = 2,293)	0.2 (4)	0.2 (2)
Hepatobiliary: liver (N = 2,144)	0.3 (6)	0.8 (6)
Anorectal: resection (N = 2,103)	0.0 (1)	0.0 (0)
Musculoskeletal: fracture repair (N = 2,065)	0.1 (3)	0.3 (3)
Biopsy skin and soft tissue (N = 2,014)	0.1 (2)	0.2 (1)

ACS NSQIP = American College of Surgeons National Surgical Quality Improvement Program.

stroke as the dependent dichotomous variable. Age was dichotomized into ≥62 yr based on the determination of maximum sensitivity and specificity. The derivation cohort logistic regression model included 309,512 (88.4%) of the patients and demonstrated the following independent predictors of perioperative stroke ($P < 0.05$): age ≥62 yr, myocardial infarction within 6 months of surgery, preoperative acute renal failure, history of stroke (per the previously stated definition), preoperative dialysis, hypertension requiring medication, history of transient ischemic attack, severe chronic obstructive pulmonary disease, current smoker, and BMI 35.0–40.0 kg/m^2 (protective) (fig. 1, table 3). The missing data elements were mainly due to missing races documented in this national deidentified data set. The Hosmer–Lemeshow test demonstrated a chi-square of 11.831 with eight degrees of freedom and $P = 0.159$. The ROC AUC was 0.82 ± 0.01. Somers' Dxy in the original sample was 0.64. The bootstrap Dxy was 0.65 for the training sample and 0.63 for the test sample, which indicates very good validation. The unweighted and weighted risk scores were based on the 10 independent predictors. The unweighted risk scores demonstrated a ROC AUC of 0.80 ± 0.01 for the derivation cohort and 0.78 ± 0.02 for the validation cohort. The weighted risk score for the derivation cohort ROC AUC was 0.81 ± 0.01 and 0.80 ± 0.02 for the validation cohort. Because the 95% CIs overlapped for the unweighted and weighted derivation cohorts, we chose to use the unweighted risk scores to build a risk index classification system. The risk index classes are as follows: low risk, two or fewer risk factors; medium risk, three to four risk factors; and high risk, five or more risk factors. Risk classes were chosen based on increasing incidence and odds ratio of perioperative stroke (table 4).

30-day Mortality Analysis: Matched Cohort

Four hundred fifty-five perioperative stroke patients were matched in a one-to-one ratio to nonperioperative stroke patients based on the previously derived propensity score. The matched cohort revealed no significant associations in the univariate analysis of the preoperative predictors of stroke (table 5). However, univariate analysis demonstrated that perioperative stroke was associated with an 8-fold increase in perioperative mortality within 30 days (95% CI, 4.6–12.6). The absolute risk increase of mortality after stroke was 21% in the comorbidity-matched cohort and 24% in the derivation cohort.

Table 2. Preoperative Patient Characteristics of the Derivation Cohort

Risk Factor	Entire Cohort, n (%)	No Stroke, n (%)	Yes Stroke, n (%)	*P* Value	Odds Ratio (95% CI)
Totals	350,031	349,546	485	—	—
Male sex	139,393 (40%)	139,175 (40%)	218 (45%)	0.02	1.2 (1.0–1.5)
ASA 3, 4, or 5	348,801 (99%)	127,094 (37%)	404 (84%)	<0.001	8.8 (6.9–11.2)
Race: white*	248,089 (71%)	247,729 (78%)	360 (80%)	0.11	1.2 (1.0–1.5)
Race: Hispanic*	26,516 (7.6%)	26,492 (8.3%)	24 (5.3%)	0.03	0.6 (0.4–0.9)
Race: black*	34,081 (9.7%)	34,033 (11%)	48 (11%)	0.88	1.0 (0.8–1.4)
Race: American Indian or Alaska Native*	3,026 (0.9%)	3,019 (0.9%)	7 (1.6%)	0.21	1.7 (0.8–3.5)
Asian or Pacific Islander*	6,843 (2.0%)	6,832 (2.1%)	11 (2.4%)	0.62	1.2 (0.6–2.1)
BMI 18.5–24.9 kg/m²*	92,747 (26%)	92,592 (27%)	155 (34%)	0.01	1.3 (1.1–1.6)
BMI 25.0–30.0 kg/m²*	106,768 (31%)	106,621 (31%)	147 (32%)	1.00	1.0 (0.8–1.2)
BMI 30.1–34.9 kg/m²*	62,200 (18%)	62,109 (18%)	91 (20%)	0.55	1.1 (0.9–1.3)
BMI 35.0–40.0 kg/m²*	34,785 (9.9%)	34,752 (10%)	33 (7.2%)	0.02	0.7 (0.5–0.9)
BMI >40.0 kg/m²*	43,017 (12%)	42,982 (13%)	35 (7.6%)	<0.001	0.6 (0.4–0.8)
Diabetes: oral therapy	28,098 (8.0%)	28,040 (8.0%)	58 (12%)	<0.001	1.7 (1.3–2.3)
Diabetes: insulin therapy	17,061 (4.9%)	17,003 (4.9%)	58 (12%)	<0.001	2.8 (2.1–3.7)
Current smoker	66,801 (19%)	66,697 (19%)	104 (21%)	0.19	1.2 (0.9–1.4)
Congestive heart failure	2,615 (0.7%)	2,597 (0.7%)	18 (3.7%)	<0.001	5.1 (3.2–8.3)
Myocardial infarction within 6 months of surgery	1,516 (0.4%)	1,490 (0.4%)	26 (5.4%)	<0.001	13.2 (8.9–19.7)
Hypertension requiring medication	143,088 (41%)	142,736 (41%)	352 (73%)	<0.001	3.8 (3.1–4.7)
Acute renal failure	1,712 (0.5%)	1,688 (0.5%)	24 (4.9%)	<0.001	10.7 (7.1–16.2)
Dialysis dependence	4,650 (1.3%)	4,609 (1.3%)	41 (8.5%)	<0.001	6.9 (5.0–9.5)
Chronic obstructive pulmonary disease	12,219 (3.5%)	12,149 (3.5%)	70 (14%)	<0.001	4.7 (3.6–6.0)
History of transient ischemic attack	6,208 (1.8%)	6,164 (1.8%)	44 (9.1%)	<0.001	5.6 (4.1–7.6)
History of stroke	10,327 (3.0%)	10,236 (2.9%)	91 (19%)	<0.001	7.7 (6.1–9.6)
Age ≥62 yr	113,554 (38%)	113,185 (32%)	369 (76%)	<0.001	6.6 (5.4–8.2)

* Each variable was compared against the rest of the cohort for race and body mass index grouping using Pearson chi-square.
ASA = American Society of Anesthesiologists physical status; BMI = body mass index.

Discussion

Using a prospectively gathered clinical data set, we have identified the incidence and risk factors of perioperative stroke after noncardiac, nonmajor-vascular, and nonneurologic surgery. A recent study of perioperative stroke found an incidence of perioperative stroke of 0.7% after hemicolectomy, 0.2% after hip replacement, and 0.6% after lobectomy or segmental lung resection, which increased to 1.0%, 0.3%, and 0.8%, respectively, in the population aged ≥65 yr.[5] By contrast, our overall incidence in the broad range of more than 500,000 cases in the derivation and validation cohorts was 0.1%. One interpretation is that the three surgeries studied in the Bateman *et al.* analysis[5] actually had a significantly higher incidence than did the overall population in the Nationwide Inpatient Sample. Our data confirm a higher incidence in patients undergoing these three surgeries than in the overall population and demonstrate that different procedures are associated with different risks. Another possibility is that the Nationwide Inpatient Sample overestimates the incidence of stroke because of coding issues such as misclassification. A third is that institutions included in the ACS NSQIP deliver a different level of perioperative care than do those in the Nationwide Inpatient Sample. Finally, definitions or diagnostic criteria of stroke may differ in the two populations.

A number of specific risk factors identified in Bateman *et al.* that were validated by the current study include older age,

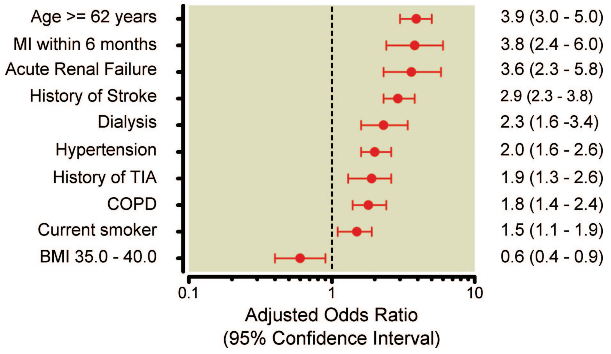

Fig. 1. Independent predictors of perioperative stroke in the noncardiac, nonneurologic surgical population. Risk factors were identified using logistic regression in a derivation cohort and subsequently validated in an independent cohort. BMI = body mass index; COPD = chronic obstructive pulmonary disease; MI = myocardial infarction; TIA = transient ischemic attack.

Table 3. Independent Predictors of Perioperative Stroke Identified by Logistic Regression Performed in the Derivation Cohort Patients

Risk Factor	B Coefficient	*P* Value	Adjusted Odds Ratio (95% CI)	Weighted Score
Age ≥62 yr	1.354	<0.001	3.9 (3.0–5.0)	7
Myocardial infarction within 6 months	1.347	<0.001	3.8 (2.4–6.0)	7
Acute renal failure	1.287	<0.001	3.6 (2.3–5.8)	7
History of stroke with or without neurologic deficits	1.080	<0.001	2.9 (2.3–3.8)	6
Pre-existing dialysis	0.843	<0.001	2.3 (1.6–3.4)	4
Hypertension requiring medications	0.702	<0.001	2.0 (1.6–2.6)	4
History of transient ischemic attack	0.618	<0.001	1.9 (1.3–2.6)	3
Chronic obstructive pulmonary disease	0.605	<0.001	1.8 (1.4–2.4)	3
Current smoker	0.378	0.002	1.5 (1.1–1.9)	2
Body mass index 35.0–40.0 kg/m^2	−0.549	0.008	0.6 (0.4–0.9)	−3

history of stroke, and renal disease.[5] Our model further identified myocardial infarction within 6 months of surgery, hypertension, history of transient ischemic attack, history of severe chronic obstructive pulmonary disease, current tobacco use, and a protective effect of BMI 35–40 kg/m^2 as independent predictors. Arrhythmias such as atrial fibrillation and valvular disease are not included as ACS NSQIP variables and thus could not be studied. It is of interest to note that BMI 35–40 kg/m^2 appeared to have a slightly protective effect against perioperative stroke, which is not consistent with recent findings in a nonsurgical community population demonstrating that obesity is a risk factor for ischemic stroke independent of race or sex.[18] However, higher BMI has been found to be protective against stroke-associated mortality in older, but not younger, stroke victims.[19]

The current investigation builds upon past studies by developing a risk index based on the independent predictors identified. Such an index can be used by clinicians to enhance vigilance for stroke in the perioperative period, serve as a source of information for patients or their families regarding stroke risk, and aid in the selection of patients for prospective studies of perioperative stroke. However, we are still limited by an incomplete understanding of the etiology of perioperative stroke, especially in the noncardiac population, in which emboli from cardiopulmonary bypass pumps and manipulations of the heart or great vessels are uncommon.[8] Data from the recent POISE Trial[20] and older studies[9,21] suggest that perioperative hypotension may be a mechanism for stroke in patients undergoing noncardiac surgery; however, the role of blood pressure in perioperative stroke has not been prospectively studied. Discontinuation of anticoagulation has also been attributed to perioperative stroke,[22] but the management of anticoagulation and antiplatelet regimens in patients at high risk for stroke has not yet been clarified. Additional progress in the prevention of stroke will depend on identifying modifiable risk factors in the perioperative period. This is especially crucial given the mortality associated with perioperative stroke and the risk of hemorrhage with thrombolytic therapy in a patient after surgery.

Strengths of this study based on the ACS NSQIP database include large numbers of cases, diverse cases, diverse patient population, clinical rather than administrative data source, and prospective data gathering. As such, the incidence of 0.1% identified in both the derivation and validation cohort of this study may be more representative than the incidence obtained from studies of administrative data sources. There are several limitations to the current analysis. First, the observational nature of the data does not allow additional detailed data collection for patients exhibiting the primary outcome. As a result, some data elements necessary to address important questions, such as the contribution of hypotension, arrhythmias, or the use of β-adrenergic blockers,[20,23,24] regarding perioperative stroke are unavailable. Additional work is required to identify intraoperative risk factors for perioperative stroke. Finally, although the data definitions are clinically relevant and rigorously followed, they could not be modified for the purposes of this study.

Table 4. Risk Index Classification System for Perioperative Stroke in the Noncardiac, Nonneurologic Surgical Population

Preoperative Risk Class	Derivation Cohort, N = 350,031		
	Total Patients, n	Stroke, % (n)	Odds Ratio (95% CI)
Low risk (≤2 risk factors)	325,630	0.1 (295)	Reference
Medium risk (3 or 4 risk factors)	23,495	0.7 (173)	8.1 (6.8–9.9)
High risk (≥5 risk factors)	906	1.9 (17)	21.1 (12.9–34.5)

Table 5. Preoperative Patient Characteristics of the Matched Stroke *vs.* No-stroke Group

Risk Factor	Matched Cohort, n (%)	No Stroke, n (%)	Yes Stroke, n (%)	*P* Value	Odds Ratio (95% CI)
Totals	910	455	455	—	—
Male sex	910 (100)	201 (44)	206 (45)	0.74	1.0 (0.8–1.4)
ASA 3, 4, or 5	909 (99)	293 (64)	376 (83)	<0.001	2.7 (2.0–3.6)
Race: white*	664 (73)	327 (77)	337 (80)	0.37	1.2 (0.8–1.6)
Race: Hispanic*	49 (5)	26 (6.1)	23 (5.4)	0.67	0.9 (0.5–1.6)
Race: black*	104 (11)	58 (14)	46 (11)	0.21	0.8 (0.5–1.2)
Race: American Indian or Alaska Native*	12 (1)	6 (1.4)	6 (1.4)	1.00	1.0 (0.3–3.0)
Asian or Pacific Islander*	18 (2)	7 (1.7)	11 (2.6)	0.40	1.6 (0.6–4.0)
BMI 18.5–24.9 kg/m^2*	308 (34)	154 (34)	154 (34)	1.00	1.0 (0.8–1.3)
BMI 25.0–30.0 kg/m^2*	294 (32)	147 (32)	147 (32)	1.00	1.0 (0.8–1.3)
BMI 30.1–34.9 kg/m^2*	180 (20)	90 (20)	90 (20)	1.00	1.0 (0.7–1.4)
BMI 35.0–40.0 kg/m^2*	64 (7)	32 (7.0)	32 (7.0)	1.00	1.0 (0.6–1.7)
BMI >40.0 kg/m^2*	64 (7)	32 (7.0)	32 (7.0)	1.00	1.0 (0.6–1.7)
Diabetes: oral therapy	99 (11)	42 (10)	57 (14)	0.08	1.5 (1.0–2.2)
Diabetes: insulin therapy	103 (11)	46 (11)	57 (14)	0.17	1.3 (0.9–2.0)
Current smoker	910 (100)	96 (21)	96 (21)	1.00	1.0 (0.7–1.4)
Congestive heart failure	910 (100)	11 (2.4)	15 (3.3)	0.43	1.4 (0.6–3.0)
Myocardial infarction within 6 months of surgery	910 (100)	23 (5.1)	23 (5.1)	1.00	1.0 (0.6–1.8)
Hypertension requiring medication	910 (100)	340 (75)	340 (75)	1.00	1.0 (0.7–1.3)
Acute renal failure	910 (100)	20 (4.4)	20 (4.4)	1.00	1.0 (0.5–1.9)
Dialysis dependence	910 (100)	36 (7.9)	36 (7.9)	1.00	1.0 (0.6–1.6)
Chronic obstructive pulmonary disease	910 (100)	64 (14)	64 (14)	1.00	1.0 (0.7–1.5)
History of transient ischemic attack	910 (100)	40 (8.8)	40 (8.8)	1.00	1.0 (0.6–1.6)
History of stroke	910 (100)	84 (19)	84 (19)	1.00	1.0 (0.7–1.4)
Age > = 62 yr	910 (100)	346 (76)	346 (76)	1.00	1.0 (0.7–1.4)
30-day all cause mortality	910 (100)	19 (4.2)	113 (25)	<0.001	7.6 (4.6–12.6)

Patients were matched using propensity score analysis in order to assess the effects of perioperative stroke on 30-day mortality.
* Each variable was compared against the rest of the cohort for race and BMI grouping using Pearson chi-square.
ASA = American Society of Anesthesiologists physical status; BMI = body mass index.

In conclusion, we have identified a 0.1% risk of perioperative stroke after noncardiac, nonmajor-vascular, and nonneurologic surgery using a large, prospectively gathered, clinical data set in a broad surgical population. The risk index for perioperative stroke developed in this study may be beneficial in both the clinical and investigative domain.

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